REMARKS/ARGUMENTS

Reconsideration of this application, as presently amended, is respectfully requested.

The Examiner objects to previous Claims 17 and 18 for misspelling the word *paclitaxel*. Pending Claims 15 and 18 have been appropriately corrected. This minor spelling mistake was an obvious typographical or clerical error. Applicants wish to thank the Examiner for noticing and bringing it to their attention.

The Examiner rejects Claims 15-18 (now Claims 15 and 18) under 35 U.S.C. § 112, first paragraph, because she finds that the specification, while being enabling for treating non-small cell type lung cancer by administering paclitaxel or carboplatin in combination with cytokine inducer compound [R-(R*,R*)]-N-[(R)-6-carboxy-N^2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine, allegedly does not reasonably provide enablement for the treatment of solid tumors of all types nor co-administration of the single cytokine inducer with any chemotherapeutic agent for reasons given on pages 3-9 of the Office action.

To expedite matters despite respectful disagreement with the merits of the rejection, Applicants are limiting the claimed method to treatment of a non-small cell lung tumor through the concurrent administration of [R-(R*,R*)]-N-[(R)-6-carboxy-N^2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine or a pharmaceutically acceptable salt thereof and a chemotherapeutic agent selected from the group consisting of paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, doxorubicin, cisplatin, carboplatin, mitomycin C, bleomycin and a combination thereof. The present amendment adds no new matter into the application. As a consequence of this amendment, there is no question that the scope of protection sought by the claims is commensurate in scope with the enablement provided to one of ordinary skill in the art by the working examples and clinical trials set forth in the disclosure.

Regarding the other enumerated chemotherapeutic agents besides paclitaxel and carboplatin for use in the treatment of NSCL tumors in combination with the claim-recited cytokine inducer, Applicants respectfully believe that the written disclosure provides sufficient enablement to the practitioner of ordinary skill in the oncology field to be able to practice the full scope of the claimed invention without undue experimentation. The specification explains

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the invention and demonstrates how to practice the claimed method with two working examples in the form of an *in vivo* standard pharmacological test procedure and a successful clinical trial. There is no reason why the practitioner would question the results or the accuracy of the statements regarding the method of treating NSCL tumors with [R-(R*, R*)]-N-[(R)-6-carboxy-N^2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine and a chemotherapeutic agent. The practitioner would reasonably expect that the same or substantially similar results shown in the application could be obtained in the use of alternative microtubular agents or macrophage activating agents besides paclitaxel and carboplatin.

On pages 4 and 5, the application teaches the preferred embodiment of the present invention in which the chemotherapeutic agent is a microtubular agent and/or a macrophage activating agent. The microtubular active compounds are illustrated as taxanes or vincristine, which include the specifically named family members of other taxanes and vinca alkaloids such as paclitaxel, docetaxel, vincristine, vinblastine and vinorelbine. Macrophage activating agents are illustrated and expressly named as doxorubicin (Adriamycin®), cisplatin, carboplatin, mitomycin C and bleomycin. Without any doubt, the successful results of the combination of paclitaxel and carboplatin in the working examples of the application would permit the ordinary practitioner to appreciate that the identified chemotherapeutic agents could readily be substituted for the paclitaxel and carboplatin without undue experimentation.

Instead of a blanket presumption of unknown predictability in the chemical or biological arts, the predictability factor refers more to the ability of the chemist or biologist to extrapolate the disclosed results to the claimed invention. It does not require a disclosure of every operable species or exemplification of each and every embodiment. The predictability factor only determines if the ordinary practitioner would have reasonable doubt as to the accuracy of treating NSCL tumors with a chemotherapeutic agent selected from the group consisting of paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, doxorubicin, cisplatin, carboplatin, mitomycin C, bleomycin and a combination thereof, and [R-(R*,R*)]-N-[(R)-6-carboxy-N^2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine as taught by the specification. Under the circumstances, reasonable doubt would not exist since a scientific basis as well as practical grounds using common sense in the oncology field would lead the

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ordinary practitioner to reasonably expect success when administering any of the alternative chemotherapeutic compounds that are taught in the application as being equivalent to paclitaxel and carboplatin. In sum, the specification provides sufficient enablement.

In view of the amendment and the above remarks, it is respectfully requested that the Examiner withdraw the rejection of the pending claims under 35 U.S.C. § 112, first paragraph.

The Examiner also rejects Claims 15-18 (now Claims 15 and 18) under 35 U.S.C. § 103(a) as being obvious over Francis *et al.* in view of U.S. Patent No. 5,545,662 for grounds given on pages 10 and 11 of the Office action. Applicants respectfully traverse the rejection for the following reasons.

There are two well-established legal principles that control the obviousness issue under the circumstances of this case. First, although a prior art combination cannot be patented even if new uses of it are found, new uses for known processes or combinations may be patented. The second principle is that combining known prior art elements is not sufficient to render a claimed invention obvious when the results would not have been predictable to the artisan.

Taking the present invention as a whole, Applicants are claiming a unique method of treating NSCL tumors using a particular combination of a specific cytokine inducer and a certain chemotherapeutic regimen. The instantly claimed method of treating NSCL tumors is a totally new concept and new utility for the cytokine inducer that was not previously described in the art. Furthermore, the synergistic results of the claim-recited combination over the tumor suppression seen with the individual chemotherapeutic agents are totally unpredictable.

The Examiner cites Francis *et al.* for teaching that the taxane compounds are active chemotherapeutic agents for NSCL cancer patients but the dose-limiting toxicity was neutropenia. The '662 patent is cited for teaching the cytokine inducer for its prior use in restoring neutrophils after cancer chemotherapy. The Examiner concludes that the combined art makes it *prima facie* obvious to use the urea compounds in combination with paclitaxel or docetaxel treatment of NSCL cancer to provide neutrophil rescue and enhanced neutrophil production to overcome neutropenic toxicity associated with treatments in NSCL patients.

Contrary to the Examiner's opinion on page 11 of the Office action, the artisan's motivation to use the claim-recited combination to restore neutrophil function or eliminate

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neutropenic toxicity in NSCL patients is irrelevant because the present invention does not relate to providing neutrophil rescue or enhancing neutrophil production. The methods of restoring bone marrow function, increasing neutrophil counts or accelerating neutrophil recovery to combat the negative side effects of cancer chemotherapy do not imply a method of treating NSCL tumors. One method does not suggest the other to one of ordinary skill in the art. They are clearly not obvious variations of the same utility. They achieve totally different end results and, as a general rule, the pharmaceutical drugs that restore bone marrow function or increase neutrophil count do not treat NSCL tumors. In fact, it is not a common property for a drug to be useful in chemotherapy and simultaneously be useful in restoring neutophil generation in the bone marrow. They are exclusive activities that are not shared by the same compounds.

Moreover, the '662 patent does not teach that the compounds of formula I would be useful to treat NSCL tumors since the compounds of formula I are not anti-tumor agents. In fact, Applicants demonstrated that the urea compound is totally devoid of anticancer activity; it did not inhibit tumor cell growth in nude mice or in tissue culture (see page 7, lines 1-6, of the application). Since the compound of formula I lacks efficacy in treating cancer and anti-tumor activity is not an inherent property, the practitioner would have no motivation to combine the urea compound with chemotherapeutic agents for the purpose of treating NSCL tumors.

In view of the absence of anticancer activity, it is surprising that the claimed combination of the cytokine inducer and the chemotherapeutic agent would have synergistic activity against H-157 (see the excellent results in Table 1 on page 6 of the application). The clinical trial with cancer patients substantiates unforeseen potency of the novel chemotherapy treatment against late stage disease.

While Francis *et al.* reported that paclitaxel had a response rate of 21% and 24% in their study with median response duration of 6 months, the complete response rate with the combined therapy of paclitaxel and carboplatin is roughly only 5%. In sharp contrast, when the representative compound of formula I was added by Applicants to their innovative therapy, the end stage cancer patients had an unexpected, significantly enhanced benefit in complete response (3 out of 6 patients), partial reduction in tumor mass (1 out of 6 patients) or stabilization of disease (1 out of 6 patients). The unexpected results show that the claimed

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method is not rendered obvious from the prior effect and use of cytokine inducers on bone marrow function and neutrophil recovery.

The fact that the compound of formula I is totally devoid of anticancer activity would negate any motivation for the oncologist to combine the compound with the microtubular or macrophage activating chemotherapeutic agents for the claim-designated purpose. The practitioner would have no reasonable expectation that the formula I compound of the claimed method could be successfully combined with the chemotherapeutic agents to significantly improve the treatment of NSCL tumors.

Since there is no reasonable expectation of success based on the inherent properties of the formula I compounds, the ordinary practitioner would not combine the teachings in the '662 patent with Francis *et al.* and arrive at the claimed method without inventive effort. As a consequence, the present method is patentable over the art.

To further distinguish the claimed method from the cited art, Claim 15 has been amended to specify that the combination of the cytokine inducer and the chemotherapeutic agent or agents has a greater suppression effect on the tumor than the effect of the chemotherapeutic agent or agents alone; and such method represents an improvement over the art (*i.e.*, an improved method) in accord with the unexpected results from the clinical trial set forth in the application.

In view of the amendment and the foregoing remarks, Applicants respectfully ask that the Examiner kindly withdraw the rejection of Claims 15 and 18 under 35 U.S.C. § 103(a) and allow the application. If any outstanding issue remains, the Examiner is invited to contact the undersigned attorney for a discussion of mutually agreeable solutions.

Accordingly, Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

WYETH

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